PI3K/mTOR Dual Inhibitor

LY3023414

Drug Discovery Platform: Cancer Cell Signaling
The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

**Key Inclusion Criteria**
- Metastatic adenocarcinoma of the prostate
- Prostate cancer progression documented by prostate-specific antigen and/or radiographic progression as defined by Prostate Cancer Working Group 2 (PCWG2)
- Prior abiraterone treatment completed
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function
- Availability of tumor tissue

**Key Exclusion Criteria**
- Prior treatment with a cytotoxic chemotherapy, a PI3K/AKT/mTOR agent, immune checkpoint inhibitors (e.g., inhibitors of CTLA4, PD-1, PD-L1), investigational new generation potent anti-androgen therapy (e.g., ARN 509), or enzalutamide. Participants may have received docetaxel in the hormone-sensitive setting
- History of seizure or any condition that may predispose to seizure
- Loss of consciousness or transient ischemic attack within 12 months
- Uncontrolled hypertension
- Insulin-dependent diabetes mellitus. Participants with type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained by oral antidiabetics as documented by hemoglobin A1c <7%

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02407054].

*This clinical trial is being conducted in the United States in partnership with SCRI Development Innovations, LLC.*

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.
A Phase II Study of the Combination of LY3023414 and Necitumumab After First-line Chemotherapy for Metastatic Squamous Non-small Cell Carcinoma of the Lung*

Key Inclusion Criteria
• Advanced stage IV squamous non-small cell carcinoma of the lung
• Progressed on one prior line of platinum-based chemotherapy in the advanced or metastatic setting (immunotherapy will not be considered a line of chemotherapy)
• Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
• Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
• Able to swallow the study drugs whole
• Resolution of side effects from prior treatment, including neuropathy, to Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or baseline (with the exception of alopecia)
• Life expectancy of ≥3 months

Key Exclusion Criteria
• Participants who have received more than one prior line of chemotherapy in the advanced or metastatic setting (immunotherapy will not be considered a line of chemotherapy)
• Prior treatment with a PI3K/mTOR inhibitor, epidermal growth factor receptor inhibitor, and/or necitumumab
• History of brain metastases unless irradiated ≥2 weeks prior to first study treatment and stable without requirement of corticosteroids
• Insulin-dependent diabetes mellitus
• Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy
• History of New York Heart Association class ≥3, Canadian Cardiovascular Society grade ≥3, corrected QT interval >450 ms, unstable angina, or myocardial infarction in 6 months prior to study drug administration
• Currently receiving treatment with therapeutic doses of warfarin sodium
• Clinical evidence of concomitant infectious conditions, including early signs of ongoing or active infection, tuberculosis, or known infection with HIV or hepatitis A, B, or C
• History of arterial or venous embolism within 3 months prior to study enrollment

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02443337].

* This clinical trial is being conducted in the United States in partnership withSCRI Development Innovations, LLC.

LY3023414 PO BID + necitumumab†

Primary endpoint: 6-month disease control rate

‡ LY3023414 and necitumumab doses are administered over a 21-day cycle. Necitumumab is administered intravenously on days 1 and 8.

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.
The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

A Phase 1 First-in-Human Dose Study of LY3023414 in Patients With Advanced Cancer*

Key Inclusion Criteria
- Advanced and/or metastatic cancer (solid tumor or lymphoma)
- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or Revised Response Criteria for Malignant Lymphoma
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life expectancy of >6 months
- Parts B2, B3, and B6: Tumor tissue available

Part A1: LY3023414 orally once daily
Part A2: LY3023414 orally twice daily

Primary endpoint: Phase 2 dose

Part B1: LY3023414 + midazolam for drug-drug interaction (advanced/metastatic cancer)
Part B2: LY3023414 + fulvestrant (advanced/metastatic breast cancer)
Part B3: LY3023414 (malignant mesothelioma)
Part B4: LY3023414 + pemetrexed/cisplatin (malignant mesothelioma)
Part B6: LY3023414 (squamous non-small cell lung cancer characterized with PI3K activation)

Key Exclusion Criteria
- Serious preexisting medical conditions
- Symptomatic central nervous system malignancy
- Part B1 only: No concomitant medications that are strong inhibitors or inducers of CYP3A4 or midazolam
- Insulin-dependent diabetes mellitus or a history of gestational diabetes mellitus

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT01655225].

* This clinical trial is being conducted globally.

† LY3023414 dose based on part A.
Target
The PI3K/mTOR (phosphoinositide 3-kinase/mammalian target of rapamycin) pathway is stimulated by a variety of growth factors and their receptors and regulates cell metabolism, cell growth, cell survival, cell proliferation, cell motility, and angiogenesis. The PI3K/AKT/mTOR pathway is thought to be one of the most frequently mutated pathways in cancer,\(^1\,^2\) leading to cancer progression and resistance to existing treatments.\(^2\,^3\)

Molecule
LY3023414 is a small molecule that has been shown in vitro to be a selective ATP-competitive inhibitor of PI3K\(\alpha\) and mTOR, DNA-PK, and other class I PI3K family members. In vitro, LY3023414 has demonstrated inhibitory activity against PI3K and mTOR in tumor cells, as well as antiproliferative activity and cell cycle effects. In addition, in vitro, LY3023414 inhibits the ability of PI3K and mTOR to phosphorylate substrates in the PI3K/mTOR pathway.\(^4\,^5\)

Clinical Development
LY3023414 is being investigated in phase I clinical trials and in clinical trials in patients with non-small cell lung cancer and prostate cancer.

References: